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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/787,030	KENNEDY, THOMAS PRESTON	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *12-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-59 are currently pending and are the subject of this Office Action. Claims 12-59 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-11 are being examined on the merits.

Information Disclosure Statement

Reference 29 on the IDS filed 2/25/2004 does not identify the journal title or year of publication of the reference. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Election/Restrictions

Applicant's election of Group I (claims 1-11) and the compounds of formula IIB wherein M is sodium and R_2 and R_3 are hydrogen in the reply filed on June 22, 2006 is acknowledged.

A search of the elected species revealed no prior art for the instantly recited methods. As such, the election of species requirement is hereby **withdrawn** and the

search has been expanded to include other species of dithiocarbamate thiolate anions of formula IIB.

Drawings

The informal drawings are not of sufficient quality to permit examination. Accordingly, replacement drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to this Office action. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action.

Applicant is given a THREE MONTH time period to submit new drawings in compliance with 37 CFR 1.81. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a). Failure to timely submit replacement drawing sheets will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to, *inter alia*, the *in vivo* sensitization of tumors to conventional chemotherapy and to the sensitization of AIDS patients to anti-retroviral therapy by administering a dithiocarbamate thiolate anion of formula IIB. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art.

There is no evidence or support in the literature that blocking the P-glycoprotein membrane extrusion pump will sensitize AIDS patients to anti-retroviral therapy. The treatment of AIDS is complex and there is no current therapy that is fully effective. The

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is

resistance of HIV to anti-retroviral therapy is mainly due to mutations in HIV-protease and HIV-reverse transcriptase, not PGP-mediated drug resistance (see Kroeger Smith *et al.*, Current Pharmaceutical Design, 2006, vol. 12, pages 1843-1856, cited for evidentiary purposes only). Loo *et al.*, also cited for evidentiary purposes, teaches that disulfiram blocks drug resistance *in vitro* but provides no evidence that disulfiram also blocks PGP-mediated drug resistance *in vivo* or is effective to sensitize AIDS patients to anti-retroviral therapy or tumors to chemotherapy (J. Natl. Cancer Inst., 2000, vol. 92, pages 898-902). Further, disulfiram is the only compound tested in Loo *et al.*

Sensitization of tumors to chemotherapy is likewise unpredictable. The instant claims imply that by blocking P-glycoprotein membrane toxin extrusion pump the dithiocarbamate thiolate anions of the instant claims will lead to sensitization of tumors to conventional chemotherapy. However, this method requires that the chemotherapeutic drugs being used in conventional therapy be susceptible only to PGP-mediated extrusion. If resistance to chemotherapy is due to some other mechanism, it is not apparent that blocking the P-glycoprotein membrane toxin extrusion pump will have the desired effect of sensitizing tumors to chemotherapy.

Clearly then, the treatment of *in vivo* sensitization of tumors to conventional chemotherapy and the sensitization of AIDS patients to anti-retroviral therapy by administering a dithiocarbamate thiolate anion of formula IIB, particularly in humans, is extremely unpredictable.

"undue", not "experimentation".

2. The breadth of the claims

The claims are extremely broad, reciting methods of treating cancer in human cells, sensitizing tumors to chemotherapy and sensitizing AIDS patients to anti-retroviral therapy, all with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to carry out all of the claimed methods, particularly in humans. The working examples are limited only to inhibiting cancer cell proliferation *in vitro* using the specific combination of disulfiram and copper. Thus, the applicant at best has provided specific direction or guidance only for the *in vitro* inhibition of cancer cell proliferation. No reasonably specific guidance is provided concerning useful therapeutic protocols for any other diseases or therapies, especially treatment for human patients.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed compounds could be predictably used as agents to treat cancer cells, sensitize tumors to chemotherapy, and sensitize AIDS patients to anti-retroviral therapy as inferred in the claims. In fact, the

specification does not contemplate or discuss the sensitization of AIDS patients to anti-retroviral therapy. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of successes.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a method of treating cancer "in human cells" and for "sensitizing tumors to conventional cancer chemotherapy" and for "sensitizing AIDS patients to anti-retroviral therapy". This method requires the administration of a "therapeutically effective amount" of a compound of formula IIB. The patient population of claim 1, and claims dependent from claim 1, is not sufficiently made clear. The first line of the preamble implies *in vitro* treatment of human cells whereas "sensitizing tumors" to cancer chemotherapy, implies an *in vivo* method. However, it is not clear if said tumors are in a human, mouse, monkey, dog, etc. Finally, "sensitizing AIDS patients" requires the compounds be administered to an AIDS patient. Thus, claims 1-11 are indefinite

because it is not clear to who, or what, the compounds of formula IIB are being administered.

Claim 2 recites that the dithiocarbamate thiolate is in the form of a pharmaceutically acceptable salt. This is confusing because the compounds of formula IIB as recited in claim 1 are already salts. Amending the claim to recite "said dithiocarbamate thiolate anion" would overcome this rejection.

Claims 2-8 and 11 recite the limitation "wherein said dithiocarbamate thiolate" in line 1 of each respective claim. There is insufficient antecedent basis for this limitation in the claim. Claim 9, dependent from claim 7, is included in this rejection because it carries forth the limitations of claim 7 and is therefore also indefinite. Amending the claims to recite "said dithiocarbamate thiolate anion" would overcome this rejection.

In claim 3, the recitation of "per day of body weight" is *non sequitur*. (Perhaps applicant intended to recite "per day per kg of body weight"?)

Claim 10 recites the limitation "said ion" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 7, 9 and 11 are confusing with respect to what is being administered in the combination. The method of claim 1 requires the administration of a compound of formula IIB, which includes an alkali metal. However, claims 7 and 11 recite the dithiocarbamate thiolate of claim 1 is administered in combination with a metal complex (claim 7) or metal chelate (claim 11) that includes a metal and an "ion selected from the group consisting of sodium, potassium, calcium, magnesium, barium, or lithium or an anion of small molecular weight." It is not clear if the ions of claims 7, 9 and 11 are the

alkali metals already present in the compounds of formula IIB or are separate ions being administered with the metal. It is also not clear if the metal complex/chelate is a complex/chelate of the dithiocarbamate thiolate and a metal or of a complex of metal and ion.

Similarly, claim 8 is confusing with respect to the administration "in combination with a metal chelate". It is not clear what the metal is chelated to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,548,540. Although the conflicting claims are not identical, they are not patentably distinct from each other because when the method of claim 1 is used to treat cancer in a human in need thereof, the claims of the instant application and the '540 patent are identical in scope.

Claims 7-9 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,706,759. Although the conflicting claims are not identical, they are not patentably distinct from each other because when the dithiocarbamate thiolate anions of the instant method are administered in a complex with a metal, the claims of '759 and the instant application are not patentably distinct.

Conclusion

No claims are allowed. Claims 1-11 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-

272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

July 26, 2006

Ardin H. Marschel 8/1/06

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER